BRCA1 tumour suppression occurs via heterochromatin-mediated silencing.

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Public Summary:
Mutations in the tumour suppressor gene BRCA1 lead to breast and/or ovarian cancer. Here we show that loss of Brca1 in mice results in transcriptional de-repression of the tandemly repeated satellite DNA. Brca1 deficiency is accompanied by a reduction of condensed DNA regions in the genome and loss of ubiquitylation of histone H2A at satellite repeats. BRCA1 binds to satellite DNA regions and ubiquitylates H2A in vivo. Ectopic expression of H2A fused to ubiquitin reverses the effects of BRCA1 loss, indicating that BRCA1 maintains heterochromatin structure via ubiquitylation of histone H2A. Satellite DNA de-repression was also observed in mouse and human BRCA1-deficient breast cancers. Ectopic expression of satellite DNA can phenocopy BRCA1 loss in centrosome amplification, cell-cycle checkpoint defects, DNA damage and genomic instability. We propose that the role of BRCA1 in maintaining global heterochromatin integrity accounts for many of its tumour suppressor functions.

Scientific Abstract:
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